

WHAT IS CLAIMED IS:

1. A method of performing high throughput mass spectrometry screening, the method comprising:

- 5 (i) growing one or more cell;
(ii) purifying one or more non-column-separated component from the one or more cell, the purifying comprising an off-line parallel adjustment of cell growing conditions; and,
(iii) performing flow-injection analysis using electrospray tandem mass spectrometry, thereby obtaining mass-to-charge ratio data and providing high throughput mass spectrometry screening of the one or more non-column-separated component.

2. The method of claim 1, wherein step (i) occurs simultaneously with step (ii).

3. The method of claim 1, wherein at least about 100 cell colonies are screened for presence or activity of the one or more non-column-separated component in less than an hour.

4. The method of claim 1, wherein at least about 200 cell colonies are screened for presence or activity of the one or more non-column-separated component in less than an hour.

5. The method of claim 1, wherein at least about 500 cell colonies, at least about 1000 cell colonies, at least about 5000 cell colonies, at least about 10,000 cell colonies, at least about 25,000 cell colonies, or at least about 100,000 cell colonies are screened for presence or activity of the one or more non-column-separated component in less than an hour.

6. The method of claim 1, wherein at least about 200 cell colonies, at least about 1000 cell colonies, at least about 25,000 cell colonies, at least about 100,000 cell colonies, or at least about 500,000 cell colonies or more are screened for the presence or activity of the one or more non-column-separated component in about 1 day.

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7. The method of claim 5, comprising concurrently performing flow injection analysis on a plurality of cell colonies.

8. The method of claim 7, wherein the plurality of cell colonies comprises about 2 to about 1000 cell colonies.

5 9. The method of claim 8, wherein the plurality of cell colonies comprises about 5 to about 500 cell colonies.

10. The method of claim 9, wherein the plurality of cell colonies comprises about 5 to about 100 cell colonies.

10 11. The method of claim 10, wherein the plurality of cell colonies comprises about 5 to about 20 cell colonies.

12. The method of claim 1, wherein said purifying one or more non-column-separated component comprises performing step (ii) in a volatile buffer, a buffer that reduces concentration of ionic species, an ion exchange resin, or an organic solvent.

15 13. The method of claim 1, wherein the non-column-separated components are produced from whole cells, cell lysate, cell supernatant, or from reactions of purified cell enzymes with added substrates.

20 14. The method of claim 1, wherein the one or more non-column-separated component is selected from: a protein, a protein binding molecule, a carbohydrate, a carbohydrate binding molecule, a product of an enzyme catalyzed reaction, a nucleic acid, and a product of a nucleic acid catalyzed reaction.

15. The method of claim 1, wherein the one or more non-column-separated component is selected from: an enzyme, an enzyme substrate, and an enzyme product.

25 16. The method of claim 1, wherein the one or more non-column-separated component is selected from: a substrate with one or more hydrophobic moieties, an inorganic ion, an oligosaccharide, a hydrophobic molecule, atrazine, and a polyketide.

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17. The method of claim 1, wherein purifying the one or more non-column-separated component comprises attaching the one or more non-column separated components to a solid support.

18. The method of claim 17, wherein the solid support comprises one or more magnetic beads, one or more agarose beads, one or more polystyrene beads, one or more pins, a microwell plate, or a membrane.

19. The method of claim 17, wherein the one or more ~~non-separated~~ column component comprises a library of enzymes, which enzymes each comprises a tag moiety, and wherein the solid support comprises a tag binding moiety.

20. The method of claim 19, wherein the tag moiety comprises biotin, avidin, or streptavidin and the tag binding moiety comprises biotin, avidin, or streptavidin.

21. The method of claim 19, further comprising contacting the library of enzymes with one or more enzyme substrate to produce one or more product, wherein performing flow injection analysis comprises performing flow-injection analysis on the one or more product.

22. The method of claim 1, wherein the one or more non-column-separated component comprises one or more enzyme substrate and one or more product of an enzymatic reaction, the method further comprising simultaneously quantifying the amount of the one or more product of an enzyme reaction and the one or more enzyme substrate.

23. The method of claim 1, wherein performing flow injection analysis using electrospray tandem mass spectrometry comprises performing or more of: neutral loss mass spectrometry and parent ion mass spectrometry.

24. The method of claim 23, comprising performing the neutral loss mass spectrometry or the parent ion mass spectrometry on a triple quadrupole mass spectrometer.

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25. The method of claim 24, wherein performing the neutral loss mass spectrometry comprises:

- (a) scanning the one or more non column-separated-component in a first quadrupole at a specified mass range;
- 5 (b) fragmenting the one or more non-column-separated component in a second quadrupole by collision induced dissociation, thereby producing one or more neutral fragments and one or more daughter ion; and,
- (c) detecting the one or more daughter ion.

10 26. The method of claim 24, wherein performing the parent ion mass spectrometry comprises:

- (a) scanning the one or more non column-separated-component in a first quadrupole;
- (b) fragmenting the one or more non-column-separated component in a second quadrupole by collision induced dissociation; and,
- 15 (c) scanning a third quadrupole at a specified mass.

27. A method for monitoring one or more product or reactant by high throughput mass spectrometry, the method comprising:

- (i) providing a cell that has been transformed with a plasmid containing one or more member of a library of related gene sequences;
- 20 (ii) growing a cell colony or culture from the cell;
- (iii) producing the one or more product or reactant from the cell colony or culture in a biological matrix, thereby producing a non-column-separated sample,
- (iv) purifying the non-column separated sample from the biological matrix, the purifying comprising an off-line parallel adjustment of the biological matrix
- 25 used for producing the non-column separated sample; and,
- (v) monitoring the non-column separated sample by flow-injection analysis using electrospray tandem mass spectrometry, thereby monitoring the one or more product or reactant.

30 28. The method of claim 27 wherein the products/or reactants are selected from: a protein, a product of a protein reaction, a nucleic acid, and a product of a nucleic acid catalyzed reaction.

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29. The method of claim 27, wherein the products or reactants are selected from: an enzyme, and a product of an enzyme catalyzed reaction.

30. The method of claim 27, wherein step (iii) occurs simultaneously with step (iv).

5 31. The method of claim 27, wherein purifying comprises altering or adding a buffer to the biological matrix in which the non-column-separated sample is produced, thereby producing a sample that can be injected directly into a mass spectrometer for analysis of the sample.

10 32. The method of claim 27, wherein at least about 200 library members, at least about 1000 library members, at least about 5000 library members, at least about 10,000 library members, at least about 25,000 library members, or at least about 100,000 library members are screened for presence or absence of products or reactants in less than about 1 hour.

15 33. The method of claim 27, wherein at least about 200 library members, at least about 1000 library members, at least about 25,000 library members, at least about 100,000 library members, at least about 500,000 library members, or at least about 1,000,000 samples or more are screened for the presence or absence of products or reactants in about 1 day.

34. The method of claim 27, wherein the reaction is an enzyme reaction.

20 35. The method of claim 27, wherein the gene sequences encode enzymes.

25 36. The method of claim 35, wherein the one or more product or reactant comprises an enzyme substrate and a product of an enzymatic reaction, the method further comprising quantifying an amount of the enzyme substrate and an amount of the product of the enzymatic reaction.

37. The method of claim 27, wherein the cell is a bacteria.

38. The method of claim 27, wherein the purifying step occurs in reaction conditions that substantially mimic environmental cellular conditions.

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39. The method of claim 27, wherein said purifying comprises performing step (iv) in a volatile buffer, a buffer that reduces concentration of ionic species, an ion exchange resin, or an organic solvent.

5 40. The method of claim 27, wherein, the non-column-separated sample is produced using whole cells, cell lysate, cell supernatant, or a reaction of at least one purified cell enzyme with at least one substrate for the at least one cell enzyme.

10 41. The method of claim 27, wherein the non-column separated sample is selected from: a substrate with one or more hydrophobic moieties, an inorganic ion, an oligosaccharide, a hydrophobic molecule, atrazine, a lipid molecule, and a secondary metabolite.

42. The method of claim 41, wherein the secondary metabolite is a polyketide.

15 43. The method of claim 27, step (v) comprising performing neutral loss/parent ion mass spectrometry, thereby quantifying an amount of the one or more product or reactant.

44. An apparatus for high throughput mass spectrometry screening, the apparatus comprising:

- 20 (i) a cell growth plate for growing cell samples and reacting one or more of an enzyme, an enzyme substrate, and a enzyme product;
- (ii) an off-line parallel purification system coupled to or within the cell growth plate, for purifying the samples;
- (iii) an automatic sampler operably coupled to the off-line parallel purification system; and
- 25 (iii) a mass spectrometer operably coupled to the automatic sampler, said automatic sampler comprising a sample handler that transports samples from the off-line parallel purification system to the mass spectrometer for injection and analysis.

45. The apparatus of claim 44, wherein the automatic sampler transports at least about 100 samples in about an hour.

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46. The apparatus of claim 44, wherein the automatic sampler transports at least about 200 samples in about an hour.

5 47. The apparatus of claim 44, wherein the automatic sampler combines two or more samples and simultaneously injects the two or more samples into the mass spectrometer.

48. The apparatus of claim 47, wherein the mass spectrometer screens at least about 200 samples, at least about 1000 samples, at least about 5000 samples, at least about 10000 samples, at least about 25,000 samples, or at least about 100,000 samples in about an hour.

10 49. The apparatus of claim 47, wherein the mass spectrometer screens at least about 200 samples, at least about 1000 samples, at least about 25000 samples, at least about 100,000 samples, at least about 500,000 samples, or at least about 1,000,000 samples in about 1 day.

15 50. The apparatus of claim 44, wherein the rate of screening is determined by the maximum rate at which the automatic sampler transports samples between the off-line purification system and the mass spectrometer.

51. The apparatus of claim 44, wherein the offline purification system comprises a volatile buffer, a buffer that reduces concentration of ionic species, an ion exchange resin or an organic solvent.

20 52. The apparatus of claim 44, wherein the offline purification system comprises a component reactor.

53. The apparatus of claim 52, wherein the component reactor comprises an enzyme reactor.

25 54. The apparatus of claim 52, wherein the enzyme reactor comprises a solid support for immobilizing one or more components.

55. The apparatus of claim 54, wherein the one or more components comprise one or more enzyme, protein, nucleic acid, carbohydrate, lipid, sugar,

oligosaccharide, peptide, polynucleotide, small organic molecule, or secondary metabolite.

56. The apparatus of claim 54, wherein the solid support comprises one or more magnetic beads, one or more agarose beads, one or more polystyrene beads, one or more pins, or a membrane.

57. The apparatus of claim 44, wherein the cell growth plate comprises a library of related genes, which genes encode proteins or enzymes, and wherein each gene comprises a specific tag moiety.

58. The apparatus of claim 57, wherein the offline parallel purification system is within the cell growth plate and comprises a solid support, which solid support comprises a tag binding moiety, which tag bonding moiety binds to the specific tag.

59. The apparatus of claim 58, wherein the automatic sampler removes the solid support from the cell growth plate.

60. The apparatus of claim 44, wherein the mass spectrometer is an electrospray tandem mass spectrometer.

61. The apparatus of claim 44, wherein the mass spectrometer is a triple quadrupole mass spectrometer.

62. The apparatus of claim 44, further comprising a computer and software operably coupled to the apparatus for recording and analyzing data from the mass spectrometer.

63. The apparatus of claim 62, wherein the computer further comprises software for controlling the automatic sampler.

64. A method for analyzing a plurality of components, the method comprising:

- (i) providing a plurality of components; which components comprise tagged components;
- (ii) binding the tagged components to a tag binding moiety on a solid support;

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- (iii) reacting the tagged components with one or more reagents in a reaction mixture, thereby producing one or more products;
- (iv) removing the tagged components from the reaction mixture or washing the reaction mixture from the solid support; and,
- 5 (v) analyzing the tagged components, the one or more reagents, or the one or more products in a high throughput system.

65. The method of claim **64**, wherein the solid support comprises one or more magnetic beads, one or more agarose beads, one or more polystyrene beads, one or more pins, a microwell plate, or a membrane.

10 **66.** The method of claim **64**, wherein the tagged components comprises biotin, avidin or streptavidin and wherein the tag binding moiety comprises biotin, avidin, or streptavidin.

67. The method of claim **64**, wherein the components comprise enzymes, peptides, proteins, polynucleotides, carbohydrates, lipids, sugars, oligosaccharides, small
15 organic molecules, secondary metabolites, or nucleic acids.

68. The method of claim **64**, the method further comprising providing a library of genes, which genes encode one or more enzymes, which enzymes comprise the plurality of tagged components.

69. The method of claim **68**, further comprising expressing the one or
20 more tagged enzymes in one or more cells, which cells or cell supernatant comprises the reaction mixture.

70. The method of claim **69**, further comprising lysing the one or more cells.

71. The method of claim **64**, wherein the high throughput system
25 comprises a mass spectrometer.

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